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(54) Title: MANAGEMENT OF PAIN AFTER JOINT SURGERY

(57) Abstract

A method for the management of pain and immobilization resulting from joint surgery comprises administration of an analgetically effective amount of morphine-6-glucuronide (M6G) into the cavity of the joint on which surgery has been performed. Also disclosed is a pharmaceutical composition for use in the method, a single dose of such composition, a hypodermic syringe filled with this single dose, and the manufacture of a medicament for injection into the cavity of a joint on which surgery has been performed, comprising an analgetically effective amount of morphine-6-glucuronide.

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MANAGEMENT OF PAIN AFTER JOINT SURGERY

FIELD OF THE INVENTION

The present invention relates to a method for the management of pain and immobilization resulting from joint surgery, to composition for use in the method, and to the manufacture of the composition.

BACKGROUND OF THE INVENTION

Postoperative pain arising after joint surgery, for instance, knee surgery, is often severe and results in long periods of immobilization. The pain is present even at rest and is aggravated during mobilization. It hampers early postoperative mobilization and may prolong hospital care as well as outpatient care. Poor mobilization increases the risk for venous thrombosis and pulmonary embolism. Therefore reduction of pain in patients having undergone joint surgery is of major importance.

At present, patients undergoing knee or other types of orthopedic surgery most often are managed by intravenous or intramuscular morphine or other opoid-based treatments. Usually this results in short-lasting and often insufficient analgesia which may be accompanied by side effects such as nausea, vomiting, and respiratory depression. As an alternative, intravenous or intramuscular NSAIDs (non-steroid anti-inflammatory drugs), such as diclofenac, ketoprofen or ketorolac may be used. Such therapy, however, is not more efficient than administration of opoids while entailing the risk of other side effects such as gastric ulcer, asthma, and severe skin reactions. A better management of postoperative pain thus is desirable.

When given systemically morphine is transformed mainly in the liver to the 3- and 6-glucuronides. The 6-glucuronide (M6G) also is a potent opoid antagonist. It is substantially more hydrophilic than most opoids in clinical use. Therefore M6G has less tendency to penetrate the blood/brain barrier, thus decreasing the risk for adverse central nervous effects.

Morphine 6-glucuronide has been used as a preoperatively intrathecally administered analgesic to reduce postoperative pain in total hip replacement (D Grace et al., Anest. Analg. 83 (1996) 1055-9) and in knee surgery (Brit. J. Anaest. 69 (1992) 2). In both studies the observation of delayed respiratory depression cautions against such use of M6G.

OBJECTS OF THE INVENTION

It is an object of the invention to provide a method for the management of pain and immobilization resulting from joint surgery.

It is another object of the invention to provide a means for the management of pain and immobilization resulting from joint surgery.

Other objects of the invention will become apparent from the following short description of the invention, the description of preferred embodiments thereof, and the appended claims.

SUMMARY OF THE INVENTION

According to the invention is provided a method of the aforementioned kind, comprising the administration of a analgetically effective amount of morphine-6-glucuronide (M6G) into the cavity of the joint on which surgery has been performed.

Since local opoid analgesia may have a slow onset of action due to the gradual upregulation of the opoid receptors during the immediate post operative period, administration of M6G is advantageously combined with that of a local anesthetic with a short onset of action, such as lidocaine, bupivacaine, mepivacaine, and ropivacaine, providing anesthesia of medium or long duration, such as up to 3 h and longer. While the local anesthetic will exert an immediate but shorter lasting effect, the onset of action of M6G will be slower but its effect will be substantially longer than that of the local anesthetic. In combination the local anesthetic and M6G thus will exert a beneficial analgesic effect covering an extended period of time from administration and up to 48 hour or more. This long lasting analgesic effect will let the patient be mobilized earlier, and thus reduce the risk of adverse effects related to postoperative immobilization, such as venous thrombosis and pulmonary embolism. Early mobilization also translates to reduced health care costs.

An advantageous aspect of the invention is that only a fraction of M6G is needed to obtain an analgetic effect (measured at a given point in time post surgery) comparable to that obtained with morphine. In the systemic circulation the concentration of M6G will be very low; it might be even below the detection threshold. This translates to

substantially reduced central nervous effects - as well as adverse effects - which may not be even noticeable. A preferred dose for obtaining analgesia in a larger joint is from 0.05 to 10 mg. In the context of this application 'larger joint' refers to such as the knee joint, the hip joint, the shoulder joint, the elbow joint, and the ankle joint. Preferred doses for the local anesthetic with short onset vary according to its nature. For bupivacain and mepivacaine a dose of 5 mg to 100 mg is preferred.

Another advantageous aspect of the invention is the longer duration of analgesic effect obtained with M6G. This may be due to the hydrophilicity of M6G by which it is retained for a longer time in the synovial fluid of the joint to which it had been administrated. This retention also translates a substantially reduced risk for adverse central nervous effects.

Administration of M6G or of M6G in combination with a short acting local anesthetic will be into the joint capsule, either at the end of surgery before closing the capsule or upon completion of surgery.

According to still another advantageous aspect of the invention the method according to the invention comprises the administration of a non-steroid anti-inflammatory drug (NSAID), such as diclofenac, ketorolac, ketoprofen, ibuprofen, naproxen, indometacin, celecoxib and their pharmacutically acceptable salts or another nonselective NSAID (COX1/COX2) or COX2 selective drug.

According to the invention is also disclosed a pharmaceutical composition for administration to a joint comprising an amount of morphine-6-glucuronide (M6G)

effective for producing postoperative analgesia in the joint and a pharmaceutically acceptable carrier. In particular the analgesically effective amount of M6G is selected to provide an analgesic effect of at least 24 hrs, more preferred at least 48 hrs. It is also preferred for the composition to comprise a short-acting local anesthetic with a short onset of action, such as lidocaine, bupivacaine, mepivacaine, and ropivacaine and their pharmaceutically acceptable salts, but of comparatively short duration, such as a duration of up to one hour or up to three hours.

The pharmaceutically acceptable carrier may be simply saline but also other carriers are conceivable, such as an aqueous solution of hyaluronic acid which is a substitute for synnovial fluid. Thereby an extension of the duration of analgesia may be obtained.

In addition to its application in the context of joint surgery the composition of the invention has further uses, such as in treating articular inflammation.

In the following the invention will be described in more detail by reference to a preferred but not limiting embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

Example 1

Immediately upon meniscectomy (three patients; m, 35 y; m, 18 y; m, 20 y) 0.5 mg M6G and 25 mg of bupivacaine hydrochloride in 2 ml saline were injected into the articular space. The patients were mobilized for the first time already the next day, and could leave the hospital on

the 2nd day post surgery. They did not complain of any side effects, and remained substantially free of pain until being dismissed. At the same hospital patients receiving traditional intra-articular analgesia (morphine, 10 mg; bupivacaine, 25 mg) are usually dismissed on the third day after surgery, and often even later. Many of them experience adverse effects caused by morphine, such as nausea and vomiting.

Example 2

A composition of the invention for in form of a single dose intra-articular administration in connection with surgery of a larger joint was prepared by dissolving a multiple of 0.5 mg of morphine-6-glucuronide (Pharmacopeia Nordica) and 25 mg of bupivacaine hydrochloride in 2 ml of saline and filling hypodermic syringes under sterile conditions therewith. The composition is ready for use.

Example 3

A composition of the invention similar to that of Example 2, but providing extended duration of effect, was prepared by exchanging the saline for an aqueous solution of sodium hyaluronate (Sinvisc™ Roche, containing 8 mg sodium hyaluronate, 8.5 mg sodium chloride, 0.17 mg disodium hydrogen phosphate, and 0.03 mg sodium dihydrogen phosphate per ml).

C l a i m s

1. A method for the management of pain and immobilization resulting from joint surgery, comprising administration of an analgetically effective amount of morphine-6-glucuronide (M6G) into the cavity of the joint on which surgery has been performed.

2. The method of claim 1, comprising administration of an analgetically effective amount of a local anesthetic with a short onset of action.

3. The method of claim 2, wherein the local anesthetic is selected from the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine including its pharmaceutically acceptable salts.

4. The method of any of claims 1 to 3, wherein the effective amount of M6G is from 0.05 mg to 10 mg for a larger joint.

5. The method of any of claims 2 or 3, wherein the effective amount of the local anesthetic is from 1 mg to 100 mg.

6. The method of any of claims 1-5, comprising the administration of pharmacologically effective amount of a non-steroid anti-inflammatory drug (NSAID) into the cavity of the joint or systemically.

7. The method of claim 6, wherein the NSAID is selected from the group consisting of diclofenac, ketorolac, ketoprofen, ibuprofen, naproxen, indometacin, celecoxib including its pharmaceutically acceptable salts.

8. A pharmaceutical composition for injection into the cavity of a joint on which surgery has been performed, for the management of pain and immobilization resulting from joint surgery, comprising an analgetically effective amount of morphine-6-glucuronide (M6G) and a pharmaceutically acceptable carrier.

9. The composition of claim 8, wherein the amount of M6G is from 0.05 mg to 10 mg.

10. The composition of claim 8 or 9, comprising an analgetically effective amount of a local anesthetic with a short onset of action.

11. The composition of claim 10, wherein the local anesthetic is selected from the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine including its pharmaceutically acceptable salts.

12. The composition of any of claims 8 - 11, comprising a non-steroid anti-inflammatory drug (NSAID).

13. The composition of claim 12, wherein the NSAID is selected from the group consisting of diclofenac, ketorolac, ketoprofen, ibuprofen, naproxen, indometacin, celecoxib including its pharmaceutically acceptable salts.

14. The composition of any of claims 8 - 13, comprising means for retention of M6G in the joint cavity.

15. The composition of claim 14, wherein said means is hyaluronic acid or a pharmaceutically acceptable salt thereof.

16. A single dose of a pain-relieving composition for intra-articular administration comprising from 0.05 mg to 10 mg of morphine-6-glucuronide and a pharmaceutically acceptable carrier.

17. The single dose of claim 16, comprising from 1 to 100 mg of a member of the group consisting of lidocaine, bupivacaine, mepivacaine, ropivacaine and their pharmaceutically acceptable salts.

18. A hypodermic syringe filled with the single dose of claim 16 or 17.

19. The manufacture of a medicament for injection into the cavity of a joint on which surgery has been performed, comprising an analgetically effective amount of morphine-6-glucuronide (M6G).

20. The manufacture of claim 19, wherein the amount of M6G is from 0.1 mg to 10 mg.

21. The manufacture of claim 19 or 20, wherein the medicament comprises an analgetically effective amount of a local anesthetic with a short onset of action.